UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/796,040	02/05/1997	METIN COLPAN	P58126US1	8477

7590 01/30/2006

JACOBSON PRICE HOLMAN AND STERN
THE JENIFER BUILDING
400 SEVENTH STREET NW
WASHINGTON, DC 200042201

EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: **08/796,040**
Filing Date: February 05, 1997
Appellant(s): COLPAN, METIN

William E. Player
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 10, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims.

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention.

The summary of invention contained in the brief is deficient because the instant claims do not include all of the limitations described therein. First, all of the claims are not limited to a directly tandem linkage between the first two steps and the third and fourth steps as required at the end of the first paragraph of appellant's "Summary." Secondly, in the fourth paragraph of appellant's "Summary" the advantage of a single buffer being usable for two separate steps is not specifically included as a claim limitation. And thirdly, in the seventh paragraph of appellant's "Summary" the technical advantage of tandem ion exchange and mineral support chromatography are described as including promotion of impurity elution under conditions wherein the desired nucleic acid product is adsorbed, also an advantage not specifically included as a claim limitation.

(6) Issues.

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims.

The brief includes a statement that claims **120-138** do not stand or fall together but fails to present reasons in support thereof. Therefore, these claims are presumed to stand or fall together.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Number	Name	Date
5,057,426	**Henco et al.**	October 15, 1991
5,075,430	**Little**	December 24, 1991

Hames et al., Nucleic Acid Hybridisation - A Practical Approach, IRL Press, Washington, DC, 1985, only title pages and text/index pages 64-65 and 235 supplied.

International Dictionary of Medicine and Biology, Vol. 1, John Wiley & Sons, New York, NY, 1986, only title pages and p. 522 supplied.

(10.1) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in

section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **120-138** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Henco et al. '426** (PTO-892 ref. **I**) in view of **Little '430** (PTO-1449 ref. **AC**), and further in view of the International Dictionary of Medicine and Biology (PTO-892 ref. **S**) and **Hames et al.** (PTO-892 ref. **R**).

The instant claims are directed to a process for DNA purification with the following steps:
i) cell lysis using an enzyme (e.g. RNase A) or using a mixture of chemical reagents (e.g. buffered SDS) and debris removal using filtration and/or centrifugation;
ii) contacting the filtrate from step i) with an anion exchange resin in buffers of low ionic strength, and elution of the DNA from the anion exchange resin by contacting with a high-ionic-strength buffer, optionally following the addition of a lower alcohol, or of polyethylene glycol, and
iv) desalting the DNA-containing solution by contacting same with a mineral support material to effect adsorption of the DNA onto the mineral support material (e.g silica gel) followed by washing the adsorbed DNA with alcoholic solutions to remove salts, and elution of DNA from the mineral adsorbent by contacting the mineral support material with a low ionic strength buffer (e.g. buffered Tris) or with water.

Henco et al. '426 discloses a four step process summarized as follows:
i) cell lysis/filtration by any one of numerous known methods including the use of detergents, proteolytic enzymes or mechanical procedures (see claim ***8***) including centrifugation (see column 6, lines 51-66);
ii) anion exchange chromatography by transferring the product solution from step i) to an anion exchange resin followed by washing with a low ionic strength buffer the intended effect of which is to remove all of the interfering substances (e.g. RNA, proteins) from long chain DNA which remains adsorbed on the column optionally in the presence of known DNA precipitants polyethylene glycol or isopropanol (see col. 12, lines 41-42);
iii) elution of the long chain DNA from the anion exchange column adsorbent with high ionic strength buffer; and
iv) desalting the DNA by one of several different methods. One method of desalting not

mentioned in the Henco disclosure is adsorption chromatography wherein a sample of DNA is applied to the column adsorbent such as silica gel in the presence of a high ionic strength buffer and separated therefrom by subsequent elution with low ionic strength buffer or water alone.

Little '430 at column 7, lines 12-45, discloses one of several examples wherein DNA is extracted from cells of various types using chaotropic ion/enzyme-mediated digestion followed by centrifugation and ultimately chromatographic separation using a commercial diatomaceous earth (Celite™) and various buffer solutions. As noted in the abstract, Little discloses the application of DNA to the adsorbent from a relative high ionic strength solution, washing to remove salts, and subsequent elution of the adsorbed DNA with a low ionic strength buffer or with water. This reference does not disclose the use of anion exchange resins to selectively retain DNA in a purification process.

To make clear the meaning of the **Henco et al. '426** disclosure two additional definitional references have been cited along with the relevant portion of Henco to provide a more complete basis for the instant rejection. The term "chaotropic" is defined in International Dictionary of Medicine and Biology, Vol. 1, at p. 522 to be a word describing an agent which " ... destroys the the order of water when dissolved in it and thereby raises the solubility of hydrophilic substances in the solution." Further definitional exemplification is provided by **Hames et al.** (Nucleic Acid Hybridisation - A Practical Approach) via the indexing of "Chaotropic agents" at p. 235, which refers to pages 64-65 wherein a list of compounds is provided at p. 65, lines 10-12 and includes i) ethylene glycol, ii) sodium perchlorate, iii) tetramethylammonium chloride, iv) tetraethylammonium chloride and v) urea. (emphasis added) The Henco reference does not make any generic reference to "chaotropic agents," but at column 8, line 61 Henco specifies "urea" as a component of the viral lysis mixture.

Applicant's combination of,
a) conventional cell lysis,
b) the physical separation of cell debris,
c) the anionic exchange chromatography of the filtrate isolated from the cell debris, and
d) finally desalting of the DNA-containing eluate form the anion exchange column by application to a chromatographic adsorbent (e.g. silica gel) to effect the desalting,
is a combination of process steps well known in the prior art and motivated generically by the

disclosures of **Henco et al. '426**, with specific desalting step details disclosed by the **Little '430** reference. As noted supra, Henco does teach the use of DNA desalting subsequent to anion exchange. The failure to teach the specific desalting method of the instant claimed method by **Henco '426** has been addressed in the instant rejection of record by combining **Henco et al. '426** with the **Little '430** reference, wherein the latter reference discloses the utility of classical chromatography adsorbents for the purpose of isolating purified DNA in solutions with low net ionic strength. For this reason applicant's claimed process has been found to be nothing more than a combination of the **Henco '426** reference with **Little et al.'430**, wherein Henco provides the motivation to combine by noting the need to desalt the high-ionic-strength solution of DNA produced by anion exchange chromatography (see column 7, lines 44-46; or col. 12, lines 42-43). The specific details of washing steps, the timing of steps, the specific selection of wash solution contents, and the physical characteristics of the anion exchange resin and mineral adsorbent (e.g., particle diameter, pore size, etc.) are deemed to be variables clearly within the purview of the ordinary practitioner seeking to optimize the Henco and Little process steps for a specific situation. Therefore, the details of adsorbent choice, or other standard performance parameters (e.g. the frequency of washes, the variation of ionic strength in wash solutions, etc.) are deemed to be the kind of variables properly within the realm of routine experimentation by an ordinary practitioner in the course of optimizing the process steps disclosed in the prior art of record. For these reasons, the instant claims, in so far as they are directed to routine changes in experimental details of the kind noted above, are deemed to lack an adequate basis for a finding of patentable distinction for any variation of the instant claimed process, as such variations are deemed to have been properly included within the scope of the noted prior art.

Therefore, the instant claimed process for DNA purification by anion exchange chromatography followed by desalting using an entirely conventional adsorption chromatographic process would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

(10.2) New Ground of Rejection.

This Examiner's Answer does not contain any new ground of rejection.

(11) Response to Argument.

Beginning at the bottom of page 4 of appellants' brief appellant argues that " ... the cited prior art does not teach or suggest obtaining a solution of 'twice purified nucleic acids' in a two stage process of ... anion exchange extraction followed by ... further purifying the once-purified nucleic acids by inorganic solid phase extraction." Appellant's subsequent conclusion that " [r]eliance on Henco and Little to meet the present claims is misplaced" is not agreed with because Henco, as noted above, teaches the option of a "desalting step" following isolation of DNA by elution from an anion exchange resin using a high ionic strength buffer: see the **'426** reference at column 7, lines 44-46, at column 8, lines 66-68, at column 12, lines 13-15, and at column 12, lines 41-44. And as noted in the rejection, the **Little '430** reference discloses that "desalting" of DNA-containing buffer solutions is readily achieved by contacting said solutions with a silica-containing adsorbent followed by washing and then elution by low ionic strength buffers or by water. Applying this desalting process to the product of Henco '426 produces the instant claimed "twice purified nucleic acids."

Appellant then argues that " ... Henco contains no motivation to modify the process disclosed in therein [SIC] by the steps "c)" and "d)" of the present claims." Appellant is respectfully requested to carefully review **Henco '426** at the specific locations wherein optional "desalting" is present as specifically noted in the immediately preceding paragraph, disclosures which examiner finds to have clearly motivated the instant combination of the primary references **Henco '426** and **Little '430**, and therefore disclosures which appear to meet the "hint" requirement repeatedly asserted by appellant.

At page 6, paragraph 2, of the brief appellant argues that
"Little provides no teaching or suggestion to supply the salient deficiencies in Henco." However, because appellant has not defined the "salient deficiencies," so examiner is unable to determine the basis for this criticism by appellant's brief. Therefore, appellant's subsequent conclusion that there is " ... no motivation to combine ..." is lacking is no more than a conclusion without a factual foundation.

In the third paragraph at page 6 of the brief, appellant argues that " ... the combination of Henco and Little is overly simplistic" but no factual basis for this argument has been presented. The following sentence criticizes Henco for using an ionic gradient elution method for

separating DNA's adsorbed on an anion exchange adsorbent. Then in the last sentence appellant asserts that "[n]o use of any material for being a chaotropic salt [SIC] is disclosed or suggested by Henco," a correct statement but misleading because as noted in the "Examiner's Answer" previously of record (Paper No. **37**), Henco does specify "urea," a known non-ionic chaotropic agent, as part of a cell lysis mixture at column 8, line 61.

Appellant, citing *In re Cocer*, apparently argues that the choice of a particular salt mixture for elution of DNA's from an anion exchanger is an important part of the instant invention, and citing *In re Hoffman*, argues further that "both the idea and the means of achieving the idea must be evidenced in the prior art in order to show obviousness." Then appellant concludes that "Little" may have accidentally used a "chaotropic agent," a conclusion which appears to be a non sequitur in light of the beginning of the argument wherein Henco is criticized.

Beginning in the second paragraph at page 8 of the brief, appellant argues that the motivational teaching provided by Henco's disclosure of optional "desalting" of high ionic strength DNA elution solutions is not contested generically, but is found to be lacking because Henco does not teach the particular desalting methodology disclosed by Little. Examiner respectfully disagrees with this conclusion because appellant appears to be applying an anticipation test, when the rejection under debate here is made under 35 U.S.C. §103(a) on the basis of obviousness.

In the third paragraph at page 8 of the brief, appellant argues that the difference between i) the concentration of salt in the DNA solutions produced by steps a) and b) herein and ii) the concentration of salt in the starting DNA solutions used in the method of Little constitutes an "unexpected step," an argument which appears to include an error in logic and therefore an argument that examiner fails to understand. Clarification is respectfully requested.

In the fourth paragraph at page 8 of the brief, appellant asserts that "[t]he statement of rejection maintains that Little [**'430**] contains motivation to substitute the three desalting methods used in Henco (column 7, lines 44 to 46) ... ," but fails to cite where within "the statement of rejection" this assertion has been made. Examiner has reviewed the rejection of record (Paper No. 09062004, mailed 09/10/2004) and, finding no such statement, has concluded that appellant may be in error.

In the first paragraph at page 9 of the brief, appellant argues that Henco and Little are "alternative separation method[s]." Examiner respectfully disagrees with this assertion and finds it to be beside the point.

In the second paragraph at page 9 of the brief, appellant argues that the instant claimed method is the first example wherein a DNA purification procedure takes advantage of "silica" [actually " Celite™ "] for a desalting step. Appellant then asserts that "... Little was not at all dealing with a desalting method ... ." Examiner respectfully disagrees, noting in Little '430's discussion of "Background of the Invention" at column 1, lines 26-35, that the problem of purification of DNA-containing mixtures " ... require costly solvent delivery systems and the reprecipitation of the isolated DNA fractions since they usually contain salt or are too dilute ... ," a clear statement of the problem of isolating DNA from salt-containing solutions and also a reason to devise a method of desalting such solutions, something which the Little '430 process does very effectively. In light of this direct quotation from the Little '430 disclosure, examiner respectfully disagrees with the conclusion stated at the bottom of page 9 of the brief to the effect that " ... the skilled artisan would not have considered using the procedure of Little as the optional desalting step of Henco." Examiner reaffirms that the combination of the Henco et al. '426 and Little '430 references cited in the rejection of record is clearly not the result of hindsight reconstruction as alleged by appellant.

In the first full paragraph at page 10 of the brief, appellant argues that Little '430 has been misinterpreted because the rejection " ... makes it appear as if Little encompasses (that is, *contemplated*) using *isolated* DNA as a starting material. Examiner respectfully disagrees with this view, referring appellant to the Little '430 reference at column 3, lines 51-62, wherein the Little process is taught to be an effective method for isolation of DNA bands from agarose gels, clearly a source of purified DNA. Therefore, appellant's paragraph bridging pages 10 and 11 of the instant response is itself misleading because it fails to understand the significance of the particular portion of Little cited in this paragraph.

In the first full paragraph at page 11 of the brief, appellant argues that the combination should be -- Little '430' in view of Henco '426 --, an interesting theory but not relevant because this combination is not before appellant and examiner in this debate.

In the second full paragraph at page 11 of the brief, appellant argues briefly "hindsight

reconstruction" citing *In re Hedges* on the basis that examiner has provided the instant combination by "picking and choosing" from within Little in order to achieve the instant subject matter by hindsight reconstruction. Examiner respectfully disagrees, and argues in response that Henco '426 teaches optional desalting as appellant has admitted, and thereby Henco has opened the door to the ordinary artisan seeking to optimize the prior art process of Henco by applying any desalting process following the anion exchange step. Although it is correct that Little '430 provides a general approach to obtaining water solutions or low salt solutions of DNA from a variety of sources some of which are prepurified and some of which are not, it is examiner's view that Little '430 is only a single reference and therefore its combination with the motivation clearly provided by Henco et al. '426 is not impermissible hindsight reconstruction. For this reason examiner does not agree that selecting the relevant portion of a general teaching is in this case an example of impermissible "picking and choosing."

In the first paragraph at page 12 of the brief, appellant argues that " ... the suggested combination would destroy the invention upon which Little was based; that is, for example, a *one*-step procedure to save time." Examiner respectfully disagrees, and finds no well argued reasoning in support of appellant's conclusion that the Little '430 invention would be destroyed by applying same following application of the Henco '426 invention.

In the second, third and fourth paragraphs at page 12 of the brief, appellant argues that the instant rejection is "fatally defective" because of a misplaced reliance on the definitional references **International Dictionary** and **Hames.** Examiner respectfully disagrees. Appellant asserts that the rejection states as follows: "that the 'Henco reference does not make specific reference to a chaotropic agent.'" Examiner questions the accuracy of this quotation, noting that the final rejection mailed 09/10/2004 states at page 4, line 3 as follows: "[t]he Henco reference does not make any generic reference to 'chaotropic agents,' but at column 8, line 61 Henco specifies 'urea' as a component of the viral lysis system." Appellant then asserts that Henco's reference to "urea" may have "accidentally" fallen within the scope of chaotropic agents, and therefore that Henco '426 is not a proper prior art reference because it fails to define urea as a functioning chaotrope. Examiner respectfully disagrees, because the presence of urea in a lysis solution can have had but one purpose that being to assist in the lysis of cell walls, a function associated with chaotropic agents in water, a combination which increases the solubility of the hydrophobic substances without which cell walls lyse and thereby release

cellular contents into the lysis solution. Therefore, examiner concludes that the presence of urea in the cell lysis mixture was not accidental, but intentional because of the vary chaotropic property imparted to the resultant solution by the presence of urea.

In the first full paragraph at page 13 of the brief, appellant argues that the rejection incorrectly responds to the assertion that the invention of Little is destroyed when the invention is defined
"... as delineated by the claims found at the end of Little." Appellant argues based on *In re Benno* that the claims are "no measure of what a patent discloses for prior art purposes of 35 U.S.C. §102 and §103. Examiner respectfully disagrees and finds that applicant's reliance on *In re Benno* is misplaced because appellant has not provided a reason or reasons in support of this conclusion here, or above. Again appellant has not effectively argued that the invention of Little is destroyed by the combination with Henco.

In the first, second, third and fourth full paragraphs at page 14 and the first two paragraphs of page 15 of the brief, appellant argues that sodium chloride is probably not a chaotrope. In reviewing the previous Examiner's Answer (Paper No. 37), examiner found at pages 12-13 a discussion of chaotropic agents and why this subject was being debated therein. Briefly appellant argued that the Henco reference failed to disclose highly chaotropic salts as components of its buffer or wash solutions while instant claims (not specified by number) specifically listed chaotropic salts as components in particular buffers. Examiner notes with interest that in instant claim **136** appellant claims an "aqueous alcoholic [wash] solution" to include " from 1 to 7M sodium perchlorate, from 1 to 7M guanidium•HCl, from 1 to 5M sodium chloride, from 1 to 6M sodium iodide, or 1M sodium chloride ... " (emphasis added). The alternative selections listed by appellant in claim **136** rely on a variety of different salts including "from 1 to 5M sodium chloride," and several other salts which appear to be more chaotropic than NaCl. Since appellant has not disclosed, claimed, or taught any critical requirement for the presence of a salt with any particular level of chaotropic character in wash solutions, examiner therefore concludes that variations in the chaotropic character of salts present in either wash or elution solutions in Henco, Little and herein are not critical and therefore discussion thereof is beside the point. This conclusion extends to appellant's subsequent remarks at pages 15-18 of the instant brief directed to where the compound "urea" may be found in the Henco reference and the significance or lack thereof.

In the first paragraph at page 19 of the brief, appellant argues that Henco is an inappropriate starting point " .. if a skilled man is going to solve the problem underlying the presently claimed invention," but fails to define the problem being referred to. Similarly in the second, third and fourth paragraphs at page 19 and all of the paragraphs of pages 20-21 and the first two paragraphs of page 22 of the brief, appellant argues that the combination of the Henco and Little references is inappropriate because of an alleged absence of motivation and because the combination fails to solve the problem underlying the instant invention. However, these arguments are not found to be convincing because appellant has not provided a clear factual basis for either conclusion.

In the third and fourth full paragraphs at page 22 and the first two paragraphs of page 23 of the brief, appellant reargues the topic of urea as a chaotropic substance. Examiner agrees that the portion of Henco which discloses urea is directed to lysis of cells, not elution. However, examiner notes an error in the first line of page 23: did appellant intend to refer to claim **136**? If so examiner notes that Little '430 discloses salt-containing alcoholic washing solutions at column 4, lines 1-35 wherein sodium chloride is present, and that Little teaches at lines 32-35 that " ... about three washes of each buffer is sufficient to lower the RNA and protein concentrations to acceptable levels." And examiner notes that Little teaches at column 4, lines 26-29, that "[i]n order to lower the RNA and protein concentrations in plasmid lysates, it is necessary to perform a sufficient number of washes using the chaotropic binding buffer and the 50% washing buffer." Moreover Little defines in detail what is meant by the term "chaotropic agent" at column 3, lines 36-42 and provides further disclosure through the end of the column.

In the third and fourth full paragraphs at page 23 and all of the paragraphs of pages 24-26 of the brief, appellant argues that the claim limitations of claims **122-126 and 129-136** are independently patentable because the instant rejection has not provided a specific prior art disclosure to meet each limitation included therein. Examiner respectfully disagrees for the following reasons.

The limitations referred to in claim **122**, "centrifugation or filtration prior to digestion," are meaningless because there is no way (a physical impossibility that) either technique will achieve the desired removal of "undesolved components" from the undesolved cells prior to cellular digestion. Clarification is respectfully requested.

The limitations in claims **123-125** wherein additional washing steps are added in between the "c)" and "d)" steps is not separately patentable because this very option is clearly disclosed by Little '430 at column 4, lines 21-25 and associated explanatory text in columns 3 and 4, including variations in ionic strength at column 4 lines 17-20 and the presence of alcohol in the buffer at column 4, lines 6-25. Washing with a perchlorate buffer as specified in claim **126** is also disclosed by Little at column 4, lines 27-32.

The limitation in claims **129-130 and 134-135** *in re* porous or non-porous anion exchange adsorbents and the particle size ranges thereof are both taught by Henco '426 at column 5, lines 22-43.

The limitation in claim **131 and 132** *in re* the mineral support and the particle size ranges thereof is in part described in Little '430 at column 2, lines 44-68 and column 3 at lines 1-19, wherein the term "kieselguhr" is defined as having as much as a 94% silica content and the particle size is also defined to include, or overlap with, the particle size ranges specified in the noted claims. Therefore, while the precise form of "silica" being used as an adsorbent in the Little patent is not identical with the "silica gel" specified in the instant claims, the difference is not deemed to be important in light of Little's teaching above noted teachings in re silica content and the teachings at column 2, lines 66-67 that "[a]ll forms of diatomaceous earth may be used in this invention," an admission that the particular type of silica-containing adsorbent being used in not a critical variable.

The limitations of claim **136** *in re* "aqueous alcoholic [buffer] solutions" used for washing are taught by Little '430 at columns 3 and 4, most particularly at column 4, lines 6-35.

Therefore, for the above noted reasons examiner respectfully disagrees with applicant's assertion in the "Grouping of Claims" and in the arguments that the variations specified in claims **122-126 and 129-136** are separately patentable. For the above noted reasons, examiner also respectfully disagrees with appellant's arguments at pages 23-25 of the instant response wherein the instant final rejection has been criticized for not meeting all of the limitations of all of the noted dependent claims.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

LECrane:lec
08/22/2005
571-272-0651

L. E. Crane, Ph.D., Esq.
Primary Patent Examiner
Technology Center 1600

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

Joseph McKane
Supervisory Patent Examiner
Technology Center 1600